In the Claims

Applicant has submitted a new complete claim set showing marked up claims with insertions indicated by underlining and deletions indicated by strikeouts and/or double bracketing.

Please amend pending claims 59-61, 65, 73, 74, 84, 85, 94, 95, 99 and 107 as noted below.

1-58 (Canceled)

59. (Currently Amended) A method of producing a nucleic acid construct that ~~provides enhanced expression of a polypeptide in a mammalian or avian subject, the~~ method comprising the steps of:

(a) determining the presence of one or more immunostimulatory unmethylated CpG motifs (CpG-S motifs) in a nucleic acid construct encoding a polypeptide; and,

(b) modifying the nucleic acid construct by:

(i) removing one or more CpG-S motifs from the nucleic acid construct; and/or

(ii) inserting one or more neutralizing CpG motifs (CpG-N motifs) into the nucleic acid construct,

wherein the modifying step (b) is performed on one or more non-essential regions of the nucleic acid construct, and/or wherein the modifying step (b) introduces one or more silent mutations into the nucleic acid construct,

~~for enhancing the expression of a therapeutic polypeptide *in vivo* wherein the polypeptide is encoded by a nucleic acid contained in a nucleic acid construct comprising, determining the CpG-N and CpG-S motifs present in the construct, removing stimulatory CpG (CpG-S) motifs and/or inserting neutralizing CpG (CpG-N) motifs,~~ thereby producing~~,~~ a nucleic acid construct providing enhanced expression of the ~~therapeutic~~ polypeptide.

60. (Currently Amended) The method of claim 59, wherein the one or more CpG-S motifs are removed by site-specific mutagenesis.

61. (Currently Amended) The method of claim 59, wherein the one or more CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

62. (Original) The method of claim 59, wherein the nucleic acid construct is an expression vector.

63. (Original) The method of claim 62, wherein the vector is a plasmid.

64. (Original) The method of claim 62, wherein the vector is a viral vector.

65. (Currently Amended) The method of claim 59, wherein the one or more CpG-S motifs in the construct comprise a motif having the formula:

$$5' X_1CGX_2 3'$$

wherein at least one nucleotide separates consecutive CpGs, X_1 is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

66. (Original) The method of claim 65, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

67. (Original) The method of claim 65, wherein the motif contains TCAACGTT.

68. (Original) The method of claim 65, wherein the motif contains GTCG(T/C)T or TGACGTT.

69. (Original) The method of claim 65, wherein the motif contains TGTCG(T/C)T.

70. (Original) The method of claim 65, wherein the motif contains TCCATGTCGTTCCTGTCGTT.

71. (Withdrawn) The method of claim 65, wherein the motif contains TCCTGACGTTCCTGACGTT.

72. (Original) The method of claim 65, wherein the motif contains TCGTCGTTTTGTCGTTTTGTCGTT.

73. (Currently Amended) The method of claim 59, wherein the ~~therapeutic~~ polypeptide is selected from the group consisting of growth factors, toxins, tumor suppressors, cytokines, apoptotic proteins, interferons, hormones, clotting factors, ligands and receptors.

74. (Currently Amended) The method of claim 59, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one ~~therapeutic~~ polypeptide.

75. (Original) The method of claim 74, wherein the regulatory sequence is a promoter.

76. (Original) The method of claim 75, wherein the promoter is insensitive to cytokine regulation.

77. (Withdrawn) The method of claim 75, wherein the promoter is a non-viral promoter.

78. (Original) The method of claim 75, wherein the promoter is a viral promoter.

79. (Original) The method of claim 78, wherein the promoter is a CMV promoter.

80. (Original) The method of claim 75, wherein the promoter is a tissue- or cell-specific promoter.

81. (Original) The method of claim 80, wherein the tissue is muscle.

82. (Original) The method of claim 80, wherein the cell is a non-immune system cell.

83. (Withdrawn) The method of claim 59, wherein therapeutic nucleic acid sequence is an antisense nucleic acid sequence.

84. (Currently Amended) A method of enhancing the expression of a polypeptide in a mammalian or avian subject, the method comprising the steps of:
(a) determining the presence of one or more immunostimulatory unmethylated CpG motifs (CpG-S motifs) in a nucleic acid construct encoding a polypeptide;
(b) modifying the nucleic acid construct by:
(i) removing one or more CpG-S motifs from the nucleic acid construct; and/or
(ii) inserting one or more neutralizing CpG motifs (CpG-N motifs) into the nucleic acid construct,
wherein the modifying step (b) is performed on one or more non-essential regions of the nucleic acid construct, and/or wherein the modifying step (b) introduces one or more silent mutations into the nucleic acid construct, and,
(c) administering the nucleic acid construct of step (b) to a mammalian or avian subject, ~~for enhancing the expression of a therapeutic polypeptide *in vivo* comprising administering to a subject a nucleic acid construct, wherein the construct is produced by determining the CpG-N and CpG-S motifs present in the construct and removing stimulatory CpG (CpG-S) motifs and/or inserting neutralizing CpG (CpG-N) motifs,~~ thereby enhancing expression of the ~~therapeutic~~ polypeptide in the subject.

85. (Currently Amended) The method of claim 84, wherein the nucleic acid construct further comprises regulatory sequences for expression of DNA in eukaryotic cells and nucleic acid sequences encoding at least one ~~therapeutic~~ polypeptide.

86. (Original) The method of claim 85, wherein the regulatory sequence is a promoter.

87. (Original) The method of claim 86, wherein the promoter is insensitive to cytokine regulation.

88. (Withdrawn) The method of claim 86, wherein the promoter is a non-viral promoter.

89. (Original) The method of claim 86, wherein the promoter is a viral promoter.

90. (Original) The method of claim 89, wherein the promoter is a CMV promoter.

91. (Original) The method of claim 86, wherein the promoter is a tissue- or cell-specific promoter.

92. (Original) The method of claim 91, wherein the tissue is muscle.

93. (Original) The method of claim 91, wherein the cell is a non-immune system cell.

94. (Currently Amended) The method of claim 84, wherein the <u>one or more</u> CpG-S motifs are removed by site-specific mutagenesis.

95. (Currently Amended) The method of claim 84, wherein the one or more CpG-N motifs are selected from the group consisting of clusters of direct repeats of CpG dinucleotides, CCG trinucleotides, CGG trinucleotides, CCGG tetranucleotides, CGCG tetranucleotides and a combination thereof.

96. (Original) The method of claim 84, wherein the nucleic acid construct is an expression vector.

97. (Original) The method of claim 96, wherein the vector is a plasmid.

98. (Original) The method of claim 96, wherein the vector is a viral vector.

99. (Currently Amended) The method of claim 84, wherein the one or more CpG-S motifs comprise a motif having the formula:

$$5' X_1CGX_2 3'$$

wherein at least one nucleotide separates consecutive CpGs, X_1, is adenine, guanine, or thymine and X_2 is cytosine, thymine, or adenine.

100. (Original) The method of claim 99, wherein the motif is selected from the group consisting of GACGTT, AGCGTT, AACGCT, GTCGTT and AACGAT.

101. (Withdrawn) The method of claim 99, wherein the motif contains TCAACGTT.

102. (Original) The method of claim 99, wherein the motif contains GTCG(T/C)T or TGACGTT.

103. (Original) The method of claim 99, wherein the motif contains TGTCG(T/C)T.

104. (Original) The method of claim 99, wherein the motif contains TCCATGTCGTTCCTGTCGTT.

105. (Withdrawn) The method of claim 99, wherein the motif contains TCCTGACGTTCCTGACGTT.

106. (Original) The method of claim 99, wherein the motif contains TCGTCGTTTTGTCGTTTTGTCGTT.

107. (Currently Amended) The method of claim 84, wherein the ~~therapeutic polypeptide is selected from the group consisting of growth factors, toxins, tumor~~ suppressors, cytokines, apoptotic proteins, interferons, hormones, clotting factors, ligands and receptors.

108. (Withdrawn) The method of claim 84, wherein therapeutic nucleic acid sequence is an antisense nucleic acid sequence.